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10/679,014	10/03/2003	David V. Goeddel	P0960R1D1C3	8921

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Goodwin Procter LLP
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EXAMINER	
BOESEN, AGNIESZKA	

ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	**Application No.** 10/679,014	**Applicant(s)** GOEDDEL ET AL.	
	Examiner AGNIESZKA BOESEN	**Art Unit** 1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 July 2008*.
2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38-41,43 and 46* is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *38-41, 43 and 46* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a)☐ All b)☐ Some * c)☐ None of:
 1.☐ Certified copies of the priority documents have been received.
 2.☐ Certified copies of the priority documents have been received in Application No. _____.
 3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
 * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
 Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
 Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Amendment filed July 8, 2008 in response to the Office Action of September 6, 2007 is acknowledged and has been entered. Claims 38, 39, 41, 43 and 46 have been amended. Claims 42, 44 and 45 have been canceled. Rejections of canceled claims are moot. Claims 38-41, 43 and 46 are pending and under examination in this Office Action.

Claim Rejections - 35 USC § 112

Rejection of claim 46 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, **is withdrawn** in view of Applicant's amendment.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejection of claims 38-41, 43, and 46 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement **is maintained**.

Applicant's arguments have been fully considered but fail to persuade. Applicants amended the claims to recite a 90% instead of 70% and 60% sequence identity with a native sequence I-TRAF polypeptide, and deleted the reference to the TRAF binding domain. Applicants argue that the specification clearly explains the properties deemed to be important for inhibiting the TRAF-mediated signaling.

In response, it is the Office's position that the present specification does not provide an adequate written description for the genus of I-TRAF polypeptides encompassed by the claims and that Applicant's amendment does not limit the claims to the functional structures of I-TRAF polypeptide for which Applicant has written description support in the specification. Amendment of claim 38 to change the reference from "TRAF" binding domain" to the "native sequence I-TRAF polypeptide" with regard to the polypeptide having at least 90% sequence identity, resulted in the increased number of possible polypeptide structures that may not necessarily have the function of interacting with TRAF 2 and inhibiting TRAF mediated signal transduction, instead of limiting the claims to the functional I-TRAF polypeptide sequences/structures. That is because claim 38 does not require that the I-TRAF binding domain must be present in the "polypeptide having at least 90% identity with a native sequence". One of the species of the native I-TRAF polypeptides is murine I-TRAF of SEQ ID NO: 1 disclosed in the present specification. SEQ ID NO: 1 is 413 amino acids in length. The specification discloses that N-terminal portion of murine I-TRAF comprising amino acids 35-236 is sufficient for interaction with TRAF2 (Example 2 on page 36). It is understood that the N-terminal portion of murine I-TRAF comprising amino acids 35-236 is necessarily required for the interaction of I-TRAF with TRAF2. The 90% of the native I-TRAF (as recited in claims 38 and 39) may not necessarily comprise the TRAF binding domain, because the 90% of murine I-TRAF comprises only 371 amino acids and those amino acid could be the C-terminal amino acids 42-413. Thus 90% of the native I-TRAF may not comprise the I-TRAF binding domain required for the interaction with TRAF2 and inhibition of TRAF-mediated signaling event. It is noted that in claim 38 the functional language "capable of inhibiting a TRAF-mediated signaling event" is recited only with regard to c) but not a) or b). Claim 39 recites the functional language with regard to all a) - g) however the recited functional language does not have support in Applicant's specification since Applicant has not shown that 90% of SEQ ID NO: 1 or SEQ ID NO: 5 has the capability of inhibiting TRAF-mediated signaling event. Additionally Applicants have not shown that polypeptides comprising amino acids 1-202 of SEQ ID NO: 5 have the capability of inhibiting TRAF-mediated signaling event. As discussed above and on the record the claimed compounds- the I-TRAF polypeptides have not been sufficiently described in terms of their structure and function, additionally Applicant specification does not provide an adequate written description support for the genus of I-TRAF polypeptides. Thus in view of the above the rejection is maintained.

The rejection of record is reiterated below

The present specification does not provide an adequate written description for the claimed methods, particularly with respect to 1) the claimed polypeptides having 90% sequence identity with the TRAF binding domain of native I-TRAF polypeptide, 2) the fragments of native I-TRAF polypeptide and the fragments of polypeptides having 90% sequence identity with the TRAF binding domain of native I-TRAF polypeptide, 3) the truncated murine I-TRAF –alpha polypeptide, 4) the equivalent part of a human I-TRAF sequence, 5) the TRAF2 binding fragments, 6) polypeptides having at least 90% sequence identity with SEQ ID NO: 5.

The claimed compounds have not been sufficiently described in terms of their structure and function. The claims refer to a function such as: capable of inhibiting a TRAF mediated signaling event resulting in modulation of TRAF mediated signal transduction. Based solely on the knowledge of the required protein function and without specific guidance with respect to the sequences of the claimed genus of protein fragments, the skilled artisan would be unable to decipher which particular sequences would have the claimed function. Claiming a product based on function does not provide sufficient description of the product as claimed.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. The Applicant has not described which part of the native I-TRAF polypeptide should be conserved in order to maintain the capability to inhibit or modulate the TRAF mediated signaling.

It has been well known that minor structural differences even among structurally related compounds or compositions can result in substantially different biological or pharmacological activities. It is known in the art that the substitution of some amino acids within the protein sequence may cause the loss of function of the protein. Thus, the large number of sequences encompassed by the current claims may or may not be effective in modulating the TRAF mediated signal transduction. See the following publications that support this unpredictability (Baker et al., Protein Structure Predication and Structural Genomics, Science (2001) Vol. 294, No. 5540, pages 93- 96; Attwood, T. The Babel of Bioinformatics, Science (2000) Vol. 290, no. 5491, pages 471-473).

The skilled artisan cannot envision the detailed structure of a genus of compounds that are contemplated in the invention. Conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Rejection of claims 38-41, 43 and 46 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement **is maintained.**

Applicant's arguments have been fully considered but fail to persuade. Applicants amended the claims to recite "a tumor cell expressing TRAF polypeptide" and the 90% sequence identity with regard to the native I-TRAF. Applicants argue that one of ordinary skill in the art could clearly practice the claimed invention without undue experimentation. Applicants disagree with Examiner that the in vitro data provided in the specification do not enable the in vivo use of the claimed methods. Applicants argue that since the specification clearly explains the mechanism of action for I-TRAF, in particular the interaction of TRAF and I-TRAF there would be no reason why the in vitro data would not translate into an in vivo setting.

In response the Office maintains that Applicant has not provided sufficient enabling disclosure to practice the claimed methods. Independent claims 38 and 41 read on in vivo methods of treating cancer, as discussed on the record. Claim 39 is interpreted as being limited to the in vitro methods. However the methods of claim 39 are not sufficiently enabled as discussed below.

With regard to claim 39 and dependent claims 40, 43 and 46, interpreted as being drawn to the in vitro methods of inhibiting TRAF mediated signaling event, Applicants' specification does not provide sufficient enabling disclosure to practice the claimed methods in any tumor cell and it does not enable to practice the methods with the truncated I-TRAF-alpha polypeptide ending with amino acids VTVLH at position 354 of (SEQ ID NO: 9) or using the polypeptide comprising amino acids 1-202 of SEQ ID NO: 5. There is lack of working examples in the specification showing that the claimed methods can be practiced with the polypeptides of d) or e).

Claims 38 and 41 read on gene therapy methods of treating cancer. As discussed in the Office Action of September 6, 2007, there is a high degree of unpredictability in the art with regard to cancer treatments employing inhibition of cellular signaling pathways. There are no teachings in the art showing successful treatment of tumor cell growth in vivo due to administering of molecules inhibiting TRAF polypeptide or inhibiting NF-kB signaling in general. Applicant's specification does not provide sufficient enabling disclosure to lead the skilled artisan to practice the claimed methods in the in vivo setting. One would be required to conduct an undue amount of experimentation to evaluate whether the introduction of I-TRAF into tumor cells in a patient would result in inhibition of TRAF mediated signal transduction and inhibition of tumor growth. The knowledge of the mechanism of I-TRAF interaction with TRAF molecules leads that skilled artisan to hypothesize that introducing I-TRAF polypeptide into a tumor cell in vivo may result in inhibition of TRAF mediated signal transduction; however this knowledge is not sufficient to provide a conclusion that the TRAF mediated signal transduction and thereby the tumor growth can be inhibited due to introducing I-TRAF (TRAF inhibitor) into a cell. Undue experimentation would be required to arrive at such as conclusion. Thus in view of the above the rejection is maintained.

The rejection of record is reiterated below

The claims are interpreted to encompass both the *in vitro* and *in vivo* methods of modulating TRAF mediated signal transduction. The claims broadly encompass a method of modulating TRAF mediated signal transduction in an unspecified broadly claimed cell type, which is interpreted to encompass all known cells. The recitation of “a method of modulation” is broadly interpreted to encompass both positive and negative modulation, including inhibition and activation of TRAF mediated signal transduction. The claimed method is drawn to modulating TRAF mediated signal transduction comprising introduction into a cell a large genus of polypeptides that encompass fragments and truncations of I-TRAF.

The nature of the present invention concerns a method for modulating TRAF-mediated signal transduction in a cell comprising introducing into a cell a nucleic acid encoding TRAF inhibitor (I-TRAF). **TRAF** has been identified as a tumor necrosis factor receptor associated protein that transduces signals from TNF receptor 2, CD40, and is required for CD40 and TNF-mediated activation of transcription factor NF-kB. **I-TRAF** has been identified as TRAF-interacting protein that regulates TRAF-mediated signal transduction. Rothe et al. (PNAS, 1996, Vol. 93, p. 8241-8246, in IDS of April 19, 2004) have shown that overexpression of I-TRAF inhibits TRAF2-mediated NF-kB activation signaled by CD40 and TNF alpha receptors. The nature of the present invention concerns the TRAF proteins that interact with the C-terminal cytoplasmic domain of Epstein-Barr virus (EBV) and transform a dominant oncogene LMP1 that activates transcription factor NF-kB, which induces up- regulation of B cell activation markers and cell growth.

Devergne et al. (Journal of Virology, 1998, Vol. 72, p. 7900-7908) has shown that signaling trough TRAF2 and TRAF5 is important for the effects of LMP1 (an EBV latent membrane protein, a dominant oncogene) on epithelial cell growth including effects on early lesions of nasopharyngeal carcinoma. Davergne et al. discusses that LMP1 stimulates TRAF1 expression that contributes to NF-kB activation, which plays an important role in antiapoptotic and transforming effects of LMP1. Kehry (Journal of Immunology, 1996, Vol. 156, p. 2345-2348) teaches that TRAF proteins associate with cytoplasmic tail of CD40, and that the CD40 receptor is expressed on antigen presenting cells, follicular dendritic cells, dendritic cells, macrophages, thymic epithelial cells, hematopoietic progenitors and some carcinoma cells.

As discussed above the claims are broadly drawn to a method of modulating TRAF mediated signal transduction in a cell. The specification contemplates treating a tumor associated with EBV virus comprising administering to a patient a TRAF inhibitor. The present claims broadly encompass the contemplated *in vivo* methods. The Examples in the specification provide guidance with respect to inhibitory effects of I-TRAF on TRAF2 and TNF-R2, and on activation of NF-kB in human embryonic kidney 293 cells (see [0118] and [0120]). Thus the current Examples provide evidence that I-TRAF has the capability to inhibit TRAF2 association with TNF-R2, and activation of NF-kB in the *in vitro* setting. However, the guidance provided in the current specification does not enable the skilled artisan to practice the current method in an *in vivo* setting in an animal.

Further, the guidance provided in the current specification does not enable the skilled artisan to practice the current method wherein the claimed modulation encompasses activation of TRAF mediated signal transduction. Additionally, the present specification does not provide an adequate enablement to allow the skilled artisan to practice the present method in all cell types. Based on the teaching of Kehry, as discussed above, because TRAF associates with CD40 that is present in antigen presenting cells and some carcinoma cells, the skilled artisan would not consider modulating TRAF mediated signaling in cells that do not express TRAF molecules. Moreover, the skilled artisan would require to conduct an undue amount of experimentation to practice the present method using all available cells that do express TRAF molecule. The skilled artisan would not intend to module TRAF mediated signal transduction in normal (non-cancerous) cells. The specification does not provide guidance with respect to how would the artisan spare modulation of TRAF signaling in normal cells. The art does not provide teachings showing that TRAF mediated cell signaling could be inhibited *in vivo* or in primary cancer cells *in vitro*. The inhibition of TRAF mediated signaling has been only shown in transformed cells lines such as in human embryonic kidney 293 cells as evidenced by Rothe et al. (PNAS, 1996, Vol. 93, p. 8241-8246). Furthermore the specification does not provide an adequate enablement to allow the skilled artisan to practice the current method comprising introducing into a cell a large genus of polypeptides that encompass fragments and truncations of I-TRAF and thereby modulating TRAF mediated signaling.

Thus considering the guidance in the present specification that is limited to practicing the present methods in the *in vitro* setting, wherein the claimed modulation is inhibition of TRAF mediated signal transduction comprising introducing a nucleic acid encoding I-TRAF polypeptide into human embryonic kidney 293 cells, in conjunction with the nature of the invention and the state of the prior art, it would require an undue amount of experimentation to practice the present method in the full scope as claimed.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to AGNIESZKA BOESEN whose telephone number is (571)272-8035. The examiner can normally be reached on Monday through Friday between 9:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Agnieszka Boesen/

Examiner, Art Unit 1648

/Bruce Campell/

Supervisory Patent Examiner, Art Unit 1648